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09/408,023	09/29/99	NARANG H	0769.00125

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ZEMAN, R	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/408,023	Narang
Examiner	**Group Art Unit**
Robert A. Zeman	1645

☒ Responsive to communication(s) filed on *Jan 15, 2001* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5-9, 11-13, 15-17, 19-21, 24-29, and 44-47* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5-9, 11-13, 15-17, 19-21, 24-29, and 44-47* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The request filed on 1-15-2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/408,023 is acceptable and a CPA has been established. An action on the CPA follows.

Specification

The use of the trademark Tween has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant's assertion that the Tween formulation is a generic formulation has been considered and not deemed to be persuasive. Tween is a registered trademark that refers denotes various formulations of polyoxyethylene sorbitans (see listing from Sigma Chemical, attached).

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-14 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Applicant argues that "the examples set forth the **exact** solutions to utilize the methods and kit of the instant invention". Applicant's argument has been considered and found not to be persuasive. While the examples do, for the most part, describe what solutions to use, Applicant fails to describe what quantity or purity of calcium phosphate is required or what is considered a "suitable buffer" and what volume and/or molarity is required for use in the claimed invention. Additionally, Applicant's limiting the claims to read on only granular calcium phosphate does not obviate the basis of this rejection.

The rejection of claims 31-43 under 35 U.S.C. 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Applicant argues that since the use of granular calcium phosphate and the filter material are sufficiently supported in the specification and the art, combining of the two would also be enabled. While there is sufficient support for use of the filter material based on Applicant's assertion that they are readily available to the public, the use of granular calcium phosphate is not supported as detailed above. Consequently, the use of both in combination would

not allow one of skill in the art to make and use the claimed invention since use of one of the aforementioned components is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 44-47, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-21, 24-33 and 37-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schenk et al. (U.S. Patent 5,593,846), in view of Alaska et al. (U.S. Patent 5,744,587) and Chu et al. (U.S. Patent 4,604,208).

Claims 1-10 and 15-18 recite methods for monitoring/concentrating liquids for the presence of disease-modified or associated proteins comprising concentrating the said proteins by contacting a solid non-buoyant granular calcium phosphate having free ionic valencies and subsequently monitoring the said concentrated protein via a myriad of conventional assays including: ELISA, electron microscopy, polymerase chain reaction (PCR) and Western blotting. Schenk et al. disclose the monitoring of Alzheimer's disease-associated protein, beta-amyloid protein (βAP), in biological fluids as means of predicting Alzheimer's disease. Schenk et al. further disclose that βAP is present in very low concentrations in biological fluids (see abstract) such as blood, cerebrospinal fluid (CSF), urine, or peritoneal fluid (see column 4 lines 39-42). Schenk et al. also disclose methods for monitoring the βAP levels in said biological fluids which include Western blotting and ELISA. While the disclosed ELISA is capable of detecting the Alzheimer's disease-associated protein at extremely low concentrations, it is disclosed by Schenk et al. that the βAP must be concentrated for use in Western blotting and assays with similar sensitivity. While Schenk et al., disclose the use of affinity purification to concentrate βAP, they do not disclose the use of solid, non-buoyant particulate matter having free ionic valencies (granular calcium phosphate) or a solid filter medium having free ionic valencies. Alaska et al. disclose the use of hydroxyapatite, which is a solid, non-buoyant particulate material, for the

binding of proteins in biological fluids, but not the use of granular calcium phosphate for the same purpose. However, as Applicant discloses on page 7 of the specification, granular calcium phosphate and hydroxyapatite are similar compounds. Both are solid, non-buoyant particulate materials with free ionic valences. Applicant further discloses that hydroxyapatite has been previously used to "purify and concentrate viruses and their related soluble antigens" (see page 7-8). Consequently, it would have been obvious to one of skill in the art to use "like" compounds in order to optimize the system. One would have a high expectation of success since, as applicant points out, hydroxyapatite and granular calcium phosphate are similar compound. Similarly, it would have been obvious to one of skill in the art to use the concentration methods disclosed by Alaska et al. in the monitoring methods disclosed by Schenk et al, because their combination would yield a higher concentration of the Alzheimer's disease-associated βAP which could then be used in more cost effective detection assays.

Claims 19-21 and 24-30 recite a methods for monitoring a liquid for the presence of biological material comprising the use of a solid filter medium having free ionic valencies and subsequently testing bound material by electron microscopy, ELISA, or Western blotting. Chu et al. disclose that the use of microporous membranes for the removal/concentration of proteins and microorganisms is well known in the art (see columns 1 -2). Additionally, Chu et al disclose the use of anionic microporous membrane (i.e. a solid filter medium with free ionic valencies) for the purification of liquids. While Chu et al. disclose the use of microporous membranes for protein/virus concentration , they do not disclose the use said membranes for the concentration

for monitoring disease associated proteins. Therefore, it would have been obvious to one of skill in the art to use the concentration methods disclosed by Chu et al. with the monitoring methods disclosed by Schenk et al, because their combination would yield a higher concentration of the Alzheimer's disease-associated βAP which could then be used in more cost effective detection assays.

Claims 31-34 and 37-43 recite methods of monitoring a liquid for the presence of disease-modified or associated proteins, a protein fragments, viruses and virus fragments utilizing a solid, non-buoyant particulate matter having free ionic valencies (granular calcium phosphate) **and** a solid filter medium having free ionic valencies. Applicant further recites that said filter medium comprises a sheet of either gauze fiber material or cotton fiber material having a pore size of 1-100 microns. As stated above, Alaska et al disclose the use of hydroxyapatite and Chu et al. disclose the use of a anionic microporous membrane for the binding of proteins and/or microorganisms in a biological fluid. Additionally, Alaska et al discloses that it is advantageous to combine the use of hydroxyapatite with other purification and concentration techniques including ultrafiltration (see Column 3, lines 57-61). Consequently, it would have been obvious for one of skill in the art to combine the use of solid, non-buoyant particulate matter having free ionic valencies (optimized for the use of granular calcium phosphate) and the anionic microporous membrane of Chu et al. with the monitoring methods of Schenk et al. One would expect the combining of the concentration methods of Chu et al. and Alaska et al. to increase efficiency since such a combination was encouraged by Alaska et al. Combination of the concentration methods of

Chu et al. and Alaska et al. with the monitoring methods of Schenk et al. would result in the need for smaller samples to be obtained from patients and the ability to use more cost effective detection assays.

Claims 11-14 recite an ELISA kit and a solid, non-buoyant particulate material (granular calcium phosphate) added for binding the proteins to be tested. For the reasons described above, the use of granular calcium would have been obvious in light of the prior art. Additionally, bundling materials to be used together in the form of a kit also would have been obvious to one of skill in the art for it would result in greater ease of use and would be more economical.

Applicant summarizes the rejections detailed above and then argues that Schenk et al., while disclosing the use of affinity purification to concentrate the beta-amyloid protein (βAP), does not disclose the use of solid buoyant particulate matter or a solid filter medium for said concentration. Applicant further argues that while Alaska et al, discloses the use of hydroxyapatite (a solid non-buoyant particulate material) for the binding of proteins in biological fluids, there are difficulties in using hydroxyapatite that are overcome by the use of granular calcium phosphate. Additionally, Applicant argues that the methods disclosed by Alaska et al. are much more complicated than the method of the claimed invention. Applicant further argues that Alaska et al, disclose methods for the removal of protein contaminants not the concentration of said proteins. Applicant continues in his argument by stating that Chu et al. discloses the use of an anionically charged microporous filter membrane for the filtration of fluids and not for the concentration of viruses or proteins and that the filter disclosed by Chu et al. is substantially

different and has not been disclosed to perform in the same manner as the membrane of the claimed invention. Applicant concludes his argument by stating that the use of an ELISA and the bundling of material in a kit would not have been obvious to one of skill in the art since it would not have been obvious to combine the disclosures of Schenk et al, Alaska et al. and Chu et al.

Applicants arguments have been considered and have been found to be unpersuasive. Applicant is correct in his assertion that Schenk et al. do not disclose the use of solid buoyant particulate matter for a solid filter medium for the concentration of beta-amyloid protein (βAP). However, Schenk et al. provide the motivation for using other methods to concentrate said protein. Applicant's assertion that the disclosure of Alaska et al. does not read on the claimed invention since hydroxyapatite and granular calcium phosphate are not similar compounds does not have a firm basis in the facts. Applicant asserts that granular calcium phosphate is superior since its use is not plagued by the same difficulties as the use of hydroxyapatite,. specifically, slow flow rate and the binding of more abundant contaminant proteins. Applicant's attention is drawn to page 8 of the specification which states "the method according to the present invention overcomes some of these difficulties by use of a medium that discriminates adsorption of albumin (in other words, proteins such as albumin are selectively not complexed as the medium **is caused to lose the charge** that allows albumin to complex). Hence, it is the non-disclosed **suitable buffer** that confers the selective binding not the granular calcium phosphate. The routine optimization of such a result effective parameter would have been obvious to one of skill in the art. With regard to Applicant's assertion that Alaska et al. is not relevant since it discloses

methods for the removal of contaminant proteins as opposed to concentrating them, it is believed that the disease associated proteins of the claimed invention are themselves "contaminant proteins" not normally found in urine. Additionally, whatever the initial motivation of Alaska et al., the result of their methods is the concentration of proteins that are present in small amounts. Consequently, it would have been obvious for one of skill in the art to use said methods to concentrate proteins for use in the methods of Schenk et al. Applicant's assertion that the methods disclosed by Alaska et al. are more complicated than, and hence different from, the claimed invention, is not based in the facts. Applicant's claims recite "comprising" which means that additional steps may be associated with the recited method steps. Consequently, Applicant's claims do not distinguish over a method that is more or less complicated than the other. With regard to Applicant's argument that the filter membranes disclosed by Chu et al. are for the filtration of fluids and not for the concentration of proteins, the use of said filter membranes concentrate proteins necessarily. Again, regardless of the initial motivation of Chu et al, since the use of the disclosed filter membranes would result in the concentration of proteins it would have been obvious for one of skill in the art to combine their use with the methods of Schenk et al. and Alaska et al. since adding additional capture steps to maximize protein concentration is standard practice in laboratories around the world. Finally, since it would have been obvious to combine the teachings of Schenk et al., Alaska et al. and Chu et al., use of an ELISA assay and the bundling of materials would have been equally obvious.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

February 20, 2001